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AdvaMed
Advanced Medical Technology Association

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Michael D. Shelby, Ph.D.
Director, CERHR
National Toxicology Program B3-09
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709-2233

Dear Dr. Shelby:

The Advanced Medical Technology Association (AdvaMed) would like to comment on NTP's CERHR Expert Panel Report on di(2-ethylhexyl) phthalate (DEHP), dated October 2000 (*Fed. Reg.*, vol. 65, no. 196, p. 60206). Our comments are limited specifically to your review, conclusions, and recommendations regarding DEHP exposure through medical products.

AdvaMed is the largest medical technology trade association in the world, supported by more than 800 medical device, diagnostic products and health information systems manufacturers of all sizes. AdvaMed member firms provide nearly 90 percent of the $68 billion of health care technology products purchased annually in the United States, and nearly 50 percent of the $159 billion purchased annually around the world.

We are pleased that the CERHR panel has adhered to current, relevant, scientific data in its review of potential human reproduction and developmental risks due to DEHP exposure. We especially applaud the CERHR panel for your recognition that concern for the immediate welfare of patients – particularly for critically ill infants – should override any theoretical or unproven risk associated with medical therapies.

The final draft reflects the substantial efforts of the expert panel as well as input from interested parties. CERHR has received correspondence from AdvaMed as well as member companies. We still believe that there are several key issues that have not been adequately addressed in the current monograph:

- The absence of clinical indication of health risks from DEHP plasticized vinyl medical products needs to be clearly stated and given prominent status in the document, not simply mentioned in a few sentences that minimize the importance of this reality.

- Exposure does not equal risk, and should not be described as such. This is a fundamental concept in toxicology, but a point that may be lost on readers less familiar with the science. Accordingly, it is a point that should be clearly reinforced throughout the document.

- The CERHR panel has not reviewed all relevant, product-specific, pre-clinical testing that occurs with product submissions to regulating agencies. At least one member company has provided the panel with clinically relevant studies conducted by non-oral routes of exposure (e.g., intravenous) which have not been fully considered in the review and drafting process.

- When the CERHR review moves from oral dosing studies in sensitive rodents to clinical, non-oral exposures, the public needs to clearly understand that the panel is applying default assumptions that may or may not reflect clinical reality. To date, we are not aware of *any* animal studies conducted by non-oral routes, and at clinically relevant DEHP or MEHP exposure levels, that demonstrate adverse effects. The general public, and especially the patient population, has the right to be clearly informed of this, especially since there are demonstrated differences in sensitivities within, and between, species. While the data may not prove the negative, they do strongly suggest that the application of default assumptions may *not* be consistent with biological reality.

Given the panel's identification of data gaps/needs, we believe the CERHR would be particularly interested in updating the DEHP evaluation as additional data that specifically addresses these identified gaps/needs becomes available. AdvaMed encourages CERHR to identify a timely process in which relevant data, as it becomes available, could be considered and incorporated in the assessment. We believe this could be one of the most important ways that the CERHR contributes to public health policies that reflect the highest adherence to current scientific evidence.

AdvaMed is aware of several new studies that will yield data specifically responsive to the data needs identified by the CERHR panel:

1. AdvaMed is co-sponsoring, with the U.S. Food and Drug Administration, a medical device utilization study that will collect usage data on the most commonly used device categories, therapies, and certain disease conditions. Such utilization information, expected within two years, is important in completing a risk/benefit review of any medical products, including those made with DEHP/vinyl.

2. Another study is underway to examine the developmental effects of intravenous (IV) exposure to DEHP in newborn rats. The study started in late November 2000, and includes oral dosing groups as well three IV groups. This study will be the only publicly available investigation we are aware of that compares oral vs. IV dosing at doses up to 600 mg/kg/day, starting at post-natal day 3-5. Notably, AdvaMed contacted a CERHR phthalate expert panel member for input on the study design, which proved invaluable.
   In addition, a US FDA toxicologist with significant expertise in DEHP has reviewed the protocol, encouraged conduct of the study, and provided highly useful comments/suggestions.

3. Finally, we are confident the CERHR is aware of the American Chemistry Council's (ACC) intended study to examine the effects of relatively high oral exposure to DEHP on sexually immature primates and the multigenerational studies in rodents (oral exposure) that are on-going. We believe the ACC sponsored studies will provide new and important information on the basic reproductive and developmental toxicology of DEHP, just as the AdvaMed studies will provide invaluable information relevant to medical products.

Support for clinically relevant, sound scientific data remains the cornerstone of the medical device industry's interest that appropriate materials are available to meet the performance, storage, and sterilization demands placed on medical products. Given the valuable data the AdvaMed studies and ACC's studies will yield, as well as likely future data from other qualified studies, we reiterate our request that CERHR identify a process to incorporate this data into its evaluation of DEHP so that public health policies reflect the most relevant, current data available.

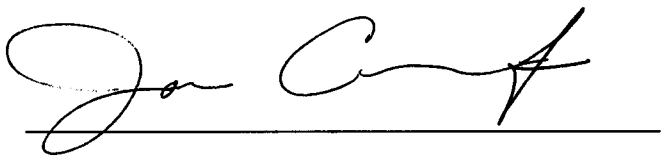
The NTP, FDA, and other national and international regulators bear a heavy responsibility for ensuring that sound, appropriate science – never conjecture and certainly not emotional debate – drive the public health policies that make safe and effective vinyl medical devices available to patients. No corroborated

clinical observations, case reports, or patient monitoring data have indicated a need for extensive clinical or epidemiological evaluation of DEHP, yet medical technology companies constantly evaluate the performance of their products, each of which has been designed with a specific material to meet a specific set of rigorous performance requirements. This is particularly important in light of the need to preserve patient access to technology where there is a notable absence of demonstrably "safer" alternative materials for vinyl medical applications. Any alternative materials should be held to the same level of scrutiny and scientific review as DEHP plasticized vinyl, which has certainly been more extensively studied than any other available medical grade material.

AdvaMed and member companies are committed to providing the best overall products for many diverse applications. We look forward to on-going dialogue with CERHR and other expert communities reviewing scientific data related to medical technologies, and we appreciate this opportunity to comment on your evaluation of DEHP.

Sincerely,

James S. Benson
Executive Vice President
Technology & Regulatory Affairs



Jon Cammack, Ph.D., D.A.B.T.
Chair, AdvaMed PVC Issue Working Group

cc: Ron Brown, FDA/CDRH
Jaro Vostal, FDA/CBER
John Moore, D.V.M., D.A.B.T.

Attachment 1

Evaluation of Reproductive Organs Following 21 Days of Repeated Intravenous and Oral Administration in Male Neonatal Rats

Type of Study: GLP

Table 1. Study Design

Treatment	Number of Animals and Sex	
	Sac at 24 d of age	Sac at 90 d of age
IV Vehicle Control	7M	9M
IV 60 mg/kg	7M	9M
IV 300 mg/kg	7M	9M
IV 600 mg/kg	7M	9M
PO Vehicle Control	7M	9M
PO 300 mg/kg	7M	9M
*PO 1000 mg/kg	7M	9M

*Dose had to be decreased to 600 mg/kg

Total Number of Animals: 112 pups

Dosing: IV; once daily for 21 consecutive days starting at 3 ± 1 days of age

Observations: Daily

Body Weight: Daily for dosage calculation (non-fasted), weekly after dosing (non-fasted) and at necropsy (non-fasted 24 day and fasted 90 day)

Organ Weights: Testes, Brain, Liver, Kidney, Spleen, Heart at 24 and 90 day

Sperm Count: At 90 day

Statistics: Body weight (i.e., weekly)
Organ weight
Organ relative to brain weight
Organ relative to body weight
Sperm Morphology/Motility and Count

Necropsy: Gross observations

Clinical Pathology: None

Histopathology: Testes (one) at 24 and 90-day
Epididymis at 90 day
Prostate at 90 day
Seminal vesicle at 90 day
Any gross pathological lesions
Sperm Morphology/Motility and Count

Tissues Preserved: Brain, Liver, Kidney, Spleen, Heart at 24 and 90 day sac